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UNCERTAINTY AND SENSITIVITY ANALYSIS ON PAT SYSTEM PERFORMANCE FOR CRYSTALLIZATION PROCESSES

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EXTENDED ABSTRACT

The introduction of the Process Analytical Technology (PAT) guidance (FDA, 2004) has resulted in increased use of process control applications and process/product quality monitoring in general. This trend is also noticeable for crystallization processes, boosted also by the fact that high quality crystalline products can be produced. The main specifications of the crystal product are usually given in terms of crystal size, crystal size distribution (CSD), shape and purity. A challenge, however, in many crystallization processes is how to obtain a uniform and reproducible CSD. Considerable efforts have been put in development of detailed models of crystallization processes in order to support the development of improved operation and control strategies. To this end, a generic systematic design of process monitoring and control (PAT) system has been developed (Samad et al., 2012). Through this framework, it is possible for a wide range of crystallization processes to generate the necessary problem-system specific model using the generic multi-dimensional model-based framework (Samad et al, 2011), the necessary set point and a PAT system design (Singh et al., 2009) including implementation of monitoring tools and control strategies in order to produce a desired product with its corresponding target crystal properties. However, thus far it has been assumed during model-based PAT system design that the exact value of the model parameters is known, for example in the nucleation and crystal growth rate expressions (Samad et al., 2012; Singh et al., 2009). These parameters are usually estimated from experimental data, often with considerable measurement errors and thus also a certain error on the estimated parameters. Consequently, there is a degree of uncertainty around the values of nucleation and crystal growth model parameters, and ideally this uncertainty should be taken into account, for example during design of a PAT system. Therefore, the impact and influence of such model parameter uncertainty on the predicted system performance needs to be quantified, as well as how it affects the system performance and possibly leads to a situation where the target specifications of the crystal product are no longer reached. The latter situation is of course not desired in a pharmaceutical production process. It is of utmost importance to develop robust model-based design tools with the necessary features to detect such potential product quality related problems.

In this work, the framework for performing the uncertainty and sensitivity analysis (Sin et al., 2009) of a PAT system has been incorporated as a new feature into the already existing overall framework (Samad et al., 2012) as shown in Figure 1. This framework (see Figure 1 (right)) contains three main steps: (i) framing of uncertainty and sensitivity analysis, (ii) reality check, and (iii) decision making. In the first step, the sources of uncertainties are identified first e.g. parameter in nucleation and crystal growth rate in crystallization process and consequencely the uncertainty analysis using Monte-Carlo simulations is carried out to test the effect of uncertainty of parameters from nucleation and crystal growth kinetic models on the predicted system performance such as solute concentration and CSD. Afterwards, the most significant parameters are identified through global sensitivity analysis techniques using Standardized Regression Coefficient (SRC) and Morris sampling

methods. The uncertainty and sensitivity analysis results are then investigated in more detail in the reality check step by confronting the numerical results with basic product-process engineering expertise. If the results of the uncertainty and sensitivity analysis are deemed not meaningful from similar or previous experiences, e.g., the estimated uncertainties in the model predictions are unrealistically high, then one has to go back to step 5.1 in order to improve the framing scenario. In the last step, the robustness of the model-based solution is evaluated by judging on a number of criteria including the probability of failure to meet target product specifications. If the target product specifications are not met due to the input uncertainties, then a solution is to be proposed in order to reduce or eliminate the probability of failure. The application of the uncertainty and sensitivity analysis will be highlighted using the one-dimensional potassium dichromate crystallization case study, where the objective is to quantify the impact of parameter uncertainty on nucleation and crystal growth models representing crystallization processes for the PAT system design. Here, the analysis is first carried out under the open loop and followed by the closed loop operation. Through analysis, it is shown that the uncertainty is minimized and the target specifications of crystal products achieved.

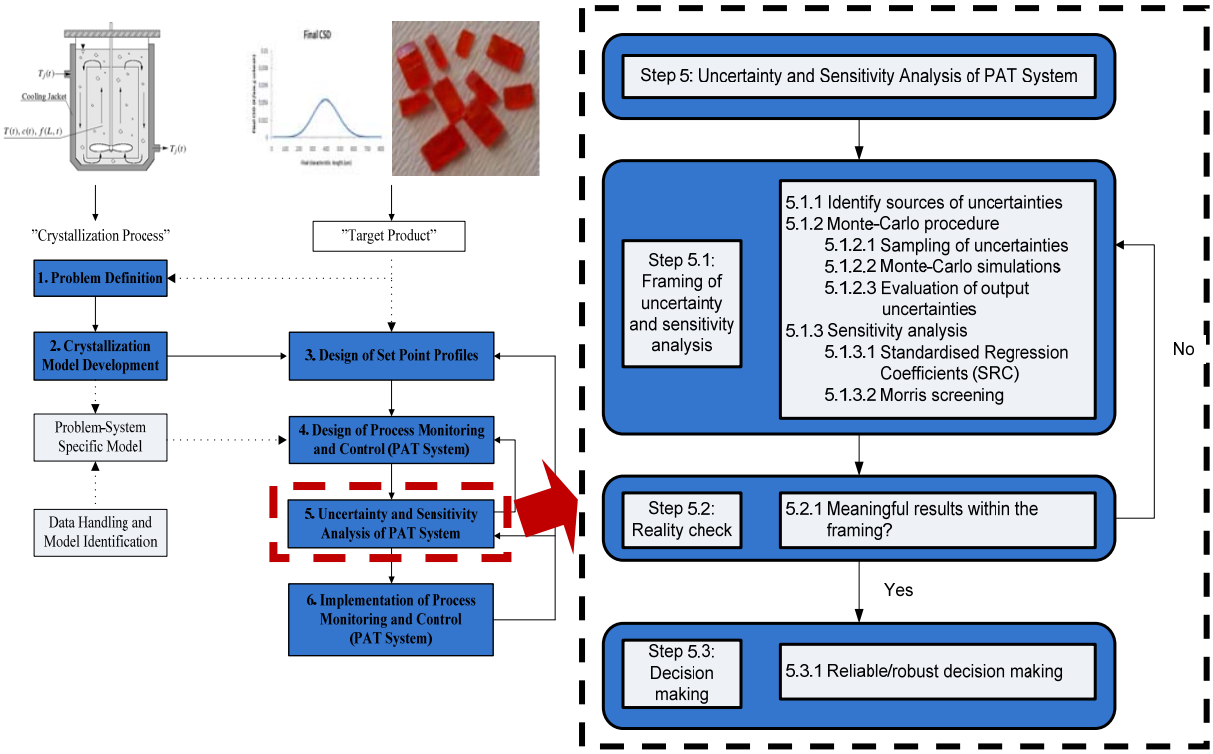

Figure 1: Incorporation of a methodology for combined uncertainty and sensitivity analysis in the framework for model-based design of product-process problems

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